

JUNE 05, 2008

Early Career Physician-Scientists Awarded \$7.1 Million to Pursue Research

Scientists who bridge the gap between basic research and clinical medicine at 14 academic medical centers will get a boost at a vital time in their career, as part of a \$7.1 million initiative from the Howard Hughes Medical Institute (HHMI).

The Early Career Physician-Scientist award will support 19 physicians who are just beginning their independent research careers, with less than two years in a tenure-track position. The award provides \$375,000 over five-years to help physician-scientists develop their research programs during a vulnerable time in their careers.

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- Peter J. Bruns

The \$75,000 per year award must be used for direct research expenses and does not support the awardees' salary. The physician-scientists often use the funds to hire a technician or purchase vital research equipment. "We think the most valuable thing we can give them is time," said Peter J. Bruns, HHMI's vice president for grants and special programs. HHMI requires that the

awardees spend at least 70 percent of their time doing research.

“Many physician-scientists drop out of research during their first few years in the field, discouraged by failed grant applications or the lack of time to focus on their research,” Bruns explained. “We want to encourage scientists who are doing important work turning basic research into treatments that will have a major impact on health.”

The award is part of a long-time push by HHMI to increase the number researchers who translate basic science discoveries into improved treatment for patients. HHMI currently supports medical, dental, and veterinary students for one or two years of full time research training through the HHMI-NIH Research Scholars Program and the HHMI Research Training Fellowships for Medical Students. Alumni of these two programs may then apply for this early career award. Top physician-scientists in the field have also joined the ranks of HHMI Investigators.

The 2008 awardees conduct research on diseases ranging from cancer to diabetes to AIDS (short summaries of the physician-scientists' research projects are provided below). They have spent an average of nine years in research and clinical training before obtaining their first academic position. They come from a variety of fields; more than half have specialized in internal medicine.

The physician-scientists in this group are a rare breed among newly minted doctors. Recent advances in biomedical research make translating basic science into patient care particularly promising. But the number of students entering translational research has remained flat. For many physician-scientists, the deciding factor in whether to pursue an academic research career is if they can successfully set up their first lab. “This solid base in the lab early in their career will allow the grantees to establish a successful research program and publish their results, which hopefully will lead to their first NIH grants,” said William Galey, HHMI's director for graduate and medical education programs. These early career awards provide essential support to physician-scientists as their start-up funds diminish and they receive increasing pressure to spend time with patients.

Physician-scientists may already be at a disadvantage competing for grants because so much of their training focuses on clinical work, which often means less time for research and fewer publications, said Joshua Roffman, a new awardee from Harvard Medical School who studies the genetic and neurological manifestations of schizophrenia. Since receiving his medical degree seven years ago, he spent four years performing clinical work and

three years conducting research. The average physician-scientist doesn't receive their first major NIH grant until age 43.

This HHMI award is “really important, especially given the ultra-competitive funding environment right now,” Roffman said, explaining this is his first major research grant. “We will be generating so much data, that it will position me as well as I could be to get (NIH) funding.”

This is the third year for the Early Career Physician-Scientist award; a total of 53 physician-scientists received a research grant through this program.

The Howard Hughes Medical Institute, a non-profit medical research organization that ranks as one of the nation's largest philanthropies, plays a powerful role in advancing biomedical research and science education in the U.S. Since the mid-1980s, HHMI has made investments of more than \$10 billion for the support, training, and education of the nation's most creative and promising scientists. The Institute commits almost \$700 million a year for research and distributes more than \$80 million in grant support for science education.

The HHMI grants program emphasizes initiatives with the power to transform graduate, undergraduate, and precollege education in the life sciences. HHMI has challenged graduate schools to change their training programs in order to shorten the time it takes to translate basic science discoveries into new medical treatments and, in partnership with the National Institutes of Health, supports a parallel initiative to encourage interdisciplinary graduate studies. It also funds International Research Scholars, promising scientists from outside the United States who are making significant contributions to understanding basic biological processes or disease mechanisms but whose careers are still developing.

HHMI's flagship program in biomedical research rests on the conviction that scientists of exceptional talent, commitment, and imagination will make fundamental biological discoveries for the betterment of human health if they receive the resources, time, and freedom to pursue challenging questions. The institute's more than 300 investigators, selected through rigorous national competitions, include 12 Nobel Prize winners and 124 members of the National Academy of Sciences. Hughes laboratories, found at 64 distinguished U.S. universities, research institutes, medical schools, and affiliated hospitals, employ hundreds of post docs and provide training opportunities for more than 1,000 graduate students each year.

The Janelia Farm Research Campus in Ashburn, Va., further extends HHMI's commitment to research and discovery. Janelia Farm scientists probe

fundamental biomedical questions best addressed through a collaborative, interdisciplinary culture. The initial research focus is the identification of the general principles that govern how information is processed by neuronal circuits and development of imaging technologies and other computational methods for image analysis. Researchers at Janelia Farm—including its most senior group leaders—engage in active bench science and work in small teams that cross disciplinary boundaries that bring chemists, physicists, computational scientists, and engineers into close collaboration with biologists.

HHMI has an endowment of approximately \$18.7 billion. Its headquarters are located in Chevy Chase, Maryland, just outside Washington, D.C.

2008 Early Career Physician-Scientist Awardees

Yvonne Chan, M.D. University of Pittsburgh School of Medicine Pittsburgh, PA HHMI Medical Fellows Program Alumna Obstructive lung diseases, such as cystic fibrosis and chronic obstructive pulmonary disease, permanently damage a person's lung tissue. Some studies suggest that the immune response to repeated or long-term lung infections may be responsible for this damage. To find out, Chan will look for evidence of prolonged immune response to specific infections in lung tissue from patients with cystic fibrosis who are undergoing lung transplants. She plans to isolate and categorize the important immune system cells called T cells to find out if they retain a memory of these bacterial infections, which would explain if these infections are more common among cystic fibrosis patients. She will then compare the activity of these T-cells to the same cells from the lung tissue of people without cystic fibrosis and see if these cells are causing the lung damage seen in this disease

John Chang, M.D. University of Pennsylvania Philadelphia, PA HHMI-NIH Research Scholars Program Alumnus When the immune system is alerted to a virus or bacteria, some white blood cells, called T cells, fight the invader. Others become memory cells, which provide long-term immunity by identifying the invader the next time it comes around. Chang has shown that a certain type of T cell, called a CD8 cell, does not divide into identical "daughter" T cells when it confronts a virus. Instead, it divides into two different cells: a T cell that fights the invader and a T cell that remembers it. He plans to see if this phenomenon, called asymmetric division, also occurs in other types of T cells, especially memory cells. The work has implications for both vaccine development and treatment of multiple diseases, including cancer and inflammatory bowel disease. Chang's discovery of asymmetric division was listed as one of the journal *Science's* Top 10 Breakthroughs of 2007.

Hyung Chun, M.D. Stanford University Medical Center Stanford, CA HHMI-NIH Research Scholars Program Alumnus Heart disease kills more than 7 million people each year worldwide. Chun is studying a molecule called apelin, which has been found to make important contributions to the

normal function of the heart and the blood vessels. He believes that the protein is also important in cardiovascular diseases. For example, he has found that apelin dramatically reduced plaque build-up in blood vessels in mice. This plaque buildup, called atherosclerosis, can lead to heart attacks in humans. He plans to study this molecule in mouse models of vascular wall disease, which may lead to better understanding and therapy for human heart disease.

Todd Fehniger, M.D., Ph.D. Washington University School of Medicine in St. Louis St. Louis, MO HHMI Medical Fellows Program Alumnus Natural killer cells live up to their name: as part of the body's innate immune system, they are among the first immune system responders that destroy cells infected by viruses or cells that have become cancerous. Harnessing the power of these natural killer cells could help physicians treat cancer and many other diseases. To do that, Fehniger wants to understand what turns natural killer cells on and off. He will focus on the role of microRNAs, small RNA molecules that turn off a protein's production in the cell by specifically targeting RNAs that make proteins. Fehniger will examine microRNA expression in both resting and activated—“armed”—natural killer cells. He also will study the role of microRNAs in regulating two molecular “weapons” of natural killer cells—granzyme B and perforin. Perforin is important for granzyme B's entry into a target cell, which then kills that cell by triggering it to commit a form of ‘suicide’ called apoptosis.

Matthew Freedman, M.D. Harvard Medical School Boston, MA HHMI-NIH Research Scholars Program Alumnus Chromosome 8 contains a region that has been implicated in prostate, colorectal, and breast cancers. But this area, called 8q24, isn't crammed with genes. It's one of the many mysterious “non-coding” regions of human DNA. So how can it affect cancer risk? That's what Freedman wants to find out. His research suggests that this “gene desert” at 8q24 influences other genes by regulating DNA transcription and is involved in modulating gene expression. Freedman wants to identify these genes, as well as discover how 8q24 is affecting them. The work has direct implications for cancer research; it also will increase knowledge about non-protein coding regions of DNA and provide a framework for studying them.

Timothy Graham, M.D. Harvard Medical School Boston, MA HHMI Medical Fellows Program Alumnus Approximately 180 million people worldwide develop type 2 diabetes, which is caused by the body's inability to respond normally to insulin, called insulin resistance. Graham has identified a protein in blood called RBP4 that is found at high levels in insulin-resistant people. He has shown that insulin resistance can be reversed in mice by lowering the blood levels of RBP4. Graham is now focused on learning how RBP4 causes insulin resistance in different tissues. He wants to know more about cell-surface receptors for the RBP4 protein. He has already shown that insulin-resistant mice have higher levels of a certain RBP4 receptor in fat tissue than healthy mice, but lower levels in the liver. He wants to know how these receptors may contribute to the development of type 2 diabetes.

Ari Green, M.D. University of California, San Francisco Medical Center San Francisco, CA HHMI Medical Fellows Program Alumnus Inflammation of the optic nerve, or optic neuritis, can be the first symptom of multiple sclerosis (MS), a degenerative disease of the central nervous system. Scientists still don't understand why patients with MS suffer irreversible injury to their nerve cells, so Green is working on using the optic nerve to understand injury to nerve cells in MS more broadly. By examining retinal injury in human tissue samples and a mouse model of MS, he has already shown that damage to the optic nerve is extremely common in MS, and the injury extends to parts of the retina that were previously thought to be unaffected in the disease. Green plans to probe the role of a specific protein in the destruction of these nerve cells, as well as initiate studies that may reveal which genes are turned on or off before a nerve cell dies.

Fred Hsieh, M.D. Cleveland Clinic Foundation Cleveland, OH HHMI-NIH Research Scholars Program Alumnus The immune system's mast cells play a central role in asthma. They release histamine and other factors that lead to inflammation and constriction in the lungs. Hsieh thinks that people with asthma might produce more stem cells that can develop into inflammatory cells like mast cells than healthy people. He hopes to find out by examining how, when, and why stem cells develop into mast cells by studying mouse models and people with asthma. Hsieh already has found that some blood-forming stem cells can produce mast cells in asthmatic lungs. Now he wants to find out if endothelial stem cells—found in the lining of the lungs—also can produce mast cells and whether they overproduce those cells in people with asthma.

Hanlee Ji, M.D. Stanford University School of Medicine Stanford, CA Research Scholars Program Alumna Multiple mutations in critical cancer genes have been implicated in the development of colon cancer, but few of these discoveries have been successfully translated for use in diagnosis, staging, or surveillance for patients with non-inherited colon cancer. Multiple issues prevent these basic genetic discoveries from being applied clinically. Ji's research program is geared towards overcoming these hurdles by using innovative genomic technologies to identify the critical genetic changes in colorectal cancer. Once identified, these genetic errors can be used in improving diagnosis and predicting drug therapeutic response. His approach relies on what is commonly referred to as "next generation" sequencing technology, a revolutionary leap in our ability to analyze DNA, integrated with novel methods and computational analysis that allow one to interrogate any part of the cancer genome for genetic errors. He is applying these technologies to study tumor samples from large groups of patients. Ultimately, his research could lead to improved diagnostic tests which allow physicians to provide more individualized management and treatments for patients with colon cancer.

Regina LaRocque, M.D. Harvard Medical School/Massachusetts General Hospital Boston, MA HHMI-NIH Research Scholars Program Alumnus Exposure to infectious diseases likely played an important role in shaping the

human genome. Cholera, a bacterial infection often linked with poverty and dirty water supplies, may have been one particularly influential disease; it may have been affecting humans as early as the seventh century, and seven cholera pandemics with high rates of mortality have swept the globe in the last three centuries. To study cholera's affect on the human genome, Larocque is working on a family-based study in Bangladesh, a region that experiences seasonal outbreaks of cholera. She has found evidence that genetic factors may affect the outcome of an individual's exposure to the cholera bacterium. Using information from this family-based study, as well as a larger study of 1,500 children with cholera, LaRocque plans to look for specific human genes related to the risk of cholera infection. Her work may provide insight into the interaction between humans and the cholera bacterium, and may also suggest new approaches to improving treatment of this continuing public health threat.

Eduardo Mendez, M.D. University of Washington Seattle, WA HHMI-NIH Research Scholars Program Alumnus Despite advances in surgery and chemotherapy, survival rates for oral cancer have not improved in the past two decades. Once the disease spreads in the body, survival rates drop. Mendez, a surgeon and epidemiologist, will soon publish the first study that has identified a "genetic signature" for poor survival rates in patients with oral cancer, and one that addresses how genetic signatures compliment clinical information in predicting survival. Now he wants to discover which genes are related specifically to the spread of oral cancer to other parts of the body. He will compare the genetics of tumors that have not spread with those that have. Mendez is interested in the genetics not only of tumor cells, but also of the non-cancerous cells that are near a tumor when it begins to spread. His results may one day allow physicians to predict which tumors are more likely to spread, information that will, in turn, affect treatment decisions.

Goutham Narla, M.D., Ph.D. The Mount Sinai School of Medicine/The Mount Sinai Hospital New York, NY HHMI Medical Fellows Program Alumnus Prostate cancer affects hundreds of thousands worldwide, and it is the second leading cause of cancer death in men in the United States. Narla has identified one of several genes associated with the disease, called KLF6. A mutated form of the gene, KLF6-SV1, promotes the growth and spread of prostate tumors, and tumors with high levels of the KLF6-SV1 protein do not respond to hormone therapy, a common prostate cancer treatment. To advance his research, Narla will study KLF6 in normal and cancerous human prostate tissue, and create a mouse model to show whether deleting the normal gene and/or adding the mutant gene increases cancer risk and tumor spread. Eventually, Narla hopes to test therapies targeted against the mutant protein.

Mark Onaitis, M.D. Duke University Medical Center Durham, NC Medical Fellows Program Alumnus More than 200,000 cases of lung cancer are diagnosed in the United States each year. One theory is that some of these cancers may be caused by adult stem cells, which live in the lungs and divide to repair them after an injury. Mutations in these important lung stem cells

could lead to cancer. Onaitis wants to understand if the two most common types of lung cancer develop after these lung stem cells are damaged. He also wants to know if lung tumors that spread quickly come from specific types of stem cells that are different from the stem cells that seed lung cancers that do not spread. Onaitis has developed a way to turn cancer-related genes off and on in these lung cells, and will use this method to test his ideas. His results could ultimately affect lung cancer treatment, as well as other diseases that have complications caused by lung injury, such as cystic fibrosis, asthma, and emphysema.

Tipu S. Puri, M.D., Ph.D. University of Chicago Chicago, IL Research Scholars Program Alumnus Chronic kidney disease affects more than 20 million people in the United States. Puri is looking for genes that might affect a person's risk for developing the disease. He has created a mouse model to study kidney disease, which he will use to identify genes that are turned off or on after kidney damage. Already, some of the mouse strains in Puri's lab show resistance to the disease, while others are more apt to develop the disorder. Puri also plans to study what happens inside kidney cells after damage occurs and whether the immune system plays a role in disease development.

Benjamin W. Purow, M.D. University of Virginia Charlottesville, VA HHMI Medical Fellows Program Alumnus Glioma is the most common—and most lethal—brain tumor; half of patients with high-grade glioma survive less than a year after their diagnosis. Purow is testing a novel treatment strategy he hopes will stop the tumor in its tracks. His previous research has found that a molecule called microRNA-7 inhibits key cancer pathways and appears to shut down the growth of glioma cells. Purow wants to know how certain cancer-related genes are stopped by microRNA-7, and whether some tumors might be more sensitive to it. He also wants to find the best way to deliver the molecule to the brain. He will test microRNA-7 as an anti-cancer therapy in mice with human gliomas with the hopes of eventually bringing it to the clinic for patients with high-grade glioma.

Joshua L. Roffman, M.D. Harvard Medical School and Massachusetts General Hospital Boston, MA HHMI-NIH Research Scholars Program Alumnus Schizophrenia affects more than two million Americans, and has no cure. Roffman is seeking a deeper understanding of schizophrenia's effects at the molecular level. His earlier work has found that patients with at least one copy of a certain form of the gene *MTHFR* have more severe symptoms than other patients with schizophrenia. This pattern is worse in patients who also have lower folate levels in their blood. Roffman will use genetic studies and brain imaging of those with and without schizophrenia to understand how the *MTHFR* protein interacts with other proteins that may be related to schizophrenia's symptoms and how these proteins affect brain function. He will also examine whether folate supplements can counteract the detrimental version of *MTHFR* and improve schizophrenia symptoms.

Allan Tsung, M.D. University of Pittsburgh Medical Center Pittsburgh, PA HHMI-NIH Research Scholars Program Alumnus When a person's liver is injured, a molecule called HMGB1 is released by liver cells to act as an alarm signal, alerting nearby immune cells of the damage. HMGB1 can activate inflammatory pathways that help repair cells, but if too much is released it may lead to further inflammation and damage. Tsung wants to tease out the cascade of events that leads to the release of HMGB1 by injured liver cells. He is focused on a family of enzymes that are sensitive to cellular changes in oxygen and calcium levels. Blocking the activity of these enzymes has reduced damage in animal models of liver inflammation. Tsung's research may ultimately help scientists understand other types of organ damage that result from lack of oxygen, including heart disease and stroke.

Arun Venkatesan, M.D., Ph.D. The Johns Hopkins University School of Medicine Baltimore, MD HHMI Medical Fellows Program Alumnus The human immunodeficiency virus (HIV) does not infect brain cells, yet it still manages to cause damage to the nervous system. About 30% of people with AIDS suffer from problems with memory, concentration, and attention. Venkatesan has found that HIV produces a protein that can damage the fibers called axons that connect nerve cells to each other. He wants to discover how the damage occurs, and to identify drugs that can prevent the destruction of axons. To do that, Venkatesan has developed new technologies to test how HIV-infected immune cells cause axon damage and whether a fatty coating called myelin protects axons from damage. He also plans to develop a cellular model of HIV infection in the brain that allows HIV-infected immune cells interact directly with axons and not with nerve cell bodies themselves. This will allow him to test potential therapies that specifically protect axons from injury. He hopes his results will lead to new therapies for AIDS, as well as diseases such as Alzheimer's and Parkinson's.

Paul B. Yu, M.D., Ph.D. Harvard Medical School and Massachusetts General Hospital Boston, MA HHMI Medical Fellows Program Alumnus In people with the rare disease fibrodysplasia ossificans progressiva (FOP), muscles, ligaments, and other soft tissues turn to bone when they are injured. Over time, this causes their arms and legs become frozen in place. The disease has no cure, but Yu wants to find one. He has created the first mouse model of FOP with a genetic mutation similar to that of affected humans, and will use it to test a possible drug therapy, which his group has developed. Yu also will try to find out which cells give rise to ossification of the bone, and whether the immune system is involved in the process. His research also has implications for heart disease as well as other disorders of abnormal bone formation.